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A direct approach to α-hydroxy and α-chloro trifluoromethyl derivatives

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This article is dedicated with respect to the memory of Professor Georges Bram

Abstract—*S*-1-Acyloxy-2,2,2-trifluoroethyl and *S*-1-chloro-2,2,2-trifluoroethyl dithiocarbonates add efficiently to various functionalised olefins to give the corresponding adducts via a radical chain reaction initiated by a small amount of lauroyl peroxide.
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As part of our studies on the development of new routes to organofluorine compounds,[1] we have recently described the use of α-acetamido trifluoromethyl xanthate **1** as a powerful reagent for the introduction of geminal amido and trifluoromethyl groups through radical addition to olefins (Fig. 1).[2,3]

In this particular reagent, the carbon–sulfur bond is weakened by an anomeric type effect due to the lone pair on the nitrogen (in essence, a lone pair–σ* interaction), and this may explain in part the remarkable efficiency of the chain process. In order to ascertain the importance of such an effect, we explored the possibility of using the analogues **2** and **3** (Fig. 1), where the interaction of the C–S σ* with the lone pair on the heteroatom is expected to be weaker. If successful, this would significantly expand the scope of this technology for the preparation of trifluoromethyl derivatives since a direct route to α-hydroxy and α-chloro trifluoromethyl structures would be at hand. Such motifs are present in a number of pharmaceutically important compounds,[4] some examples of which are given in Figure 2. Such α-trifluoromethyl alcohols are usually prepared by reaction of Rupert's reagent, or an equivalent source of trifluoromethyl anion, with an aldehyde, or by reduction of the corresponding trifluoromethyl ketone.[5]

The synthesis of xanthate **2** proved to be relatively straightforward. Thus, treatment of the hemiacetal of

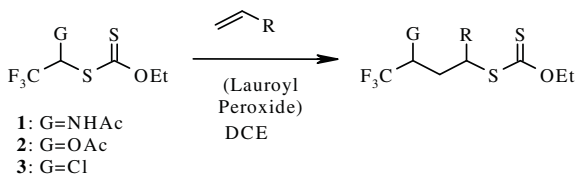

Figure 1. Synthetic route to α-amino, α-hydroxy, and α-chloro trifluoromethyl derivatives (DCE = 1,2-dichloroethane).

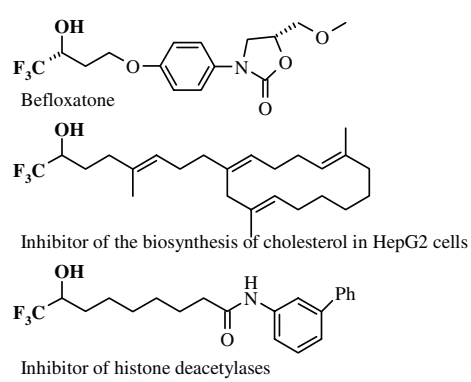

Figure 2. Some biologically active trifluoromethyl-hydroxy derivatives.

Keywords: Trifluoromethyl; Radical chain reaction; Dithiocarbonate.
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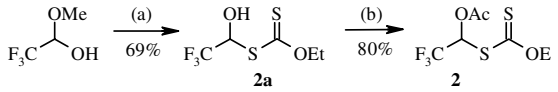
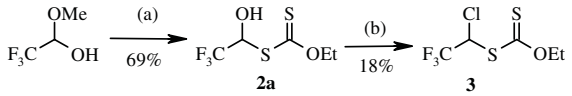


Scheme 1. Synthetic route to xanthate **2**.[6] Reagents: (a) KSC(=S)OEt, H_2SO_4, acetone; (b) Ac_2O, H_2SO_4, acetone.



Scheme 2. Synthetic route to xanthate **3**.[8] Reagents: (a) KSC(=S)OEt, H_2SO_4, acetone; (b) PCl_5.

trifluoroacetaldehyde with potassium *O*-ethylxanthate in acetone and sulfuric acid gave xanthate **2a**, which was directly acetylated with acetic anhydride and a small amount of sulfuric acid (Scheme 1). All the reagents are commercially available and the procedure is easy to scale up.

We were delighted to find that compound **2** indeed underwent the radical addition almost as efficiently as our first reagent. A high yield of adducts **2a** could be secured, merely by heating the two components together in refluxing 1,2-dichloroethane (DCE) with the portion-wise addition of a small amount of dilauroyl peroxide (DLP). The results are compiled in Table 1.[7]

As with previous additions involving xanthates, the present transformation occurs under mild, neutral conditions and is therefore compatible with a variety of functional groups. The easy synthesis of intermediate **2a** directly from the hemiacetal of trifluoroacetaldehyde and potassium *O*-ethylxanthate suggested the possibility of accessing the corresponding chloride **3**, by reaction with PCl_5 for example. In the event, xanthate **3** could be prepared from **2a** but in poor yield, as outlined in Scheme 2. Compound **3** turned out to be somewhat unstable to purification but its radical additions took place smoothly as shown by the first three examples in Table 2.[7]

We found that it was more satisfactory not to isolate the reagent or any of the intermediates for that matter, but to purify only the radical addition product **5**. The overall unoptimised yield from the hemiacetal of trifluoroacetaldehyde was quite acceptable in most cases.

The adducts lend themselves to a number of useful transformations (Scheme 3). For example, exposure of product **4b** in THF to a solution of TBAF in THF resulted in the formation of the pent-1-ene **6** in good yield (74%).[9] In the case of **5i**, derived from *N*-vinyl pyrrolidone, refluxing in chlorobenzene caused the elimination of the xanthate to give olefin **7** in quantitative yield.

Alternatively, the xanthate group in the adduct can be used to implement another radical reaction (Scheme 4). This is illustrated by the reductive cleavage using a tin free procedure we developed a few years ago,[10] as shown by the transformation of **8** and **5c** into compounds **9** and **10**, respectively.

In the case of adduct **4g**, refluxing in the same solvent with a gradual addition of peroxide induced ring-closure

Table 1. Radical additions of xanthate **2** to various olefins (Xa = S–C(=S)OEt)

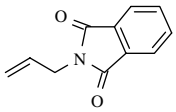
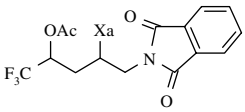
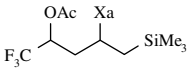
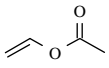
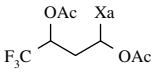
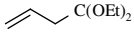
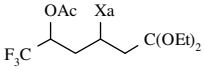
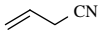
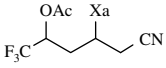
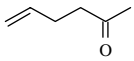
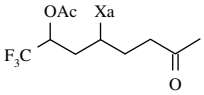
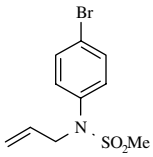
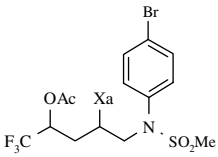
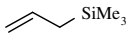
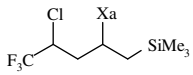
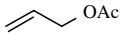
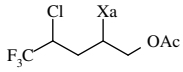
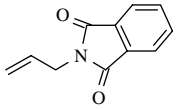
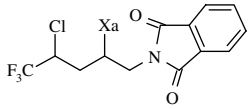
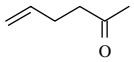
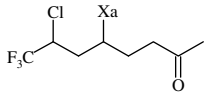
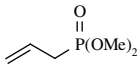
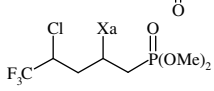
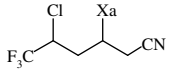
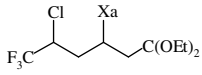
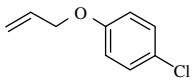
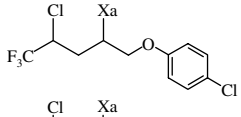
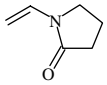
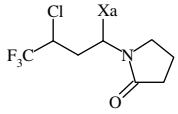
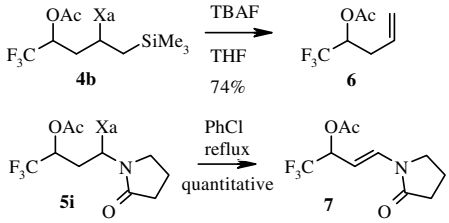
Olefin	Reaction time (h)		Adduct	Yield %	Isomeric ratio
	4.5	**4a**		78	1/1
	1.5	**4b**		80	2/3
	1.5	**4c**		79	1/1
	1.5	**4d**		82	1/1
	3	**4e**		92	3/2
	3	**4f**		88	3/2
	8	**4g**		71	1/1

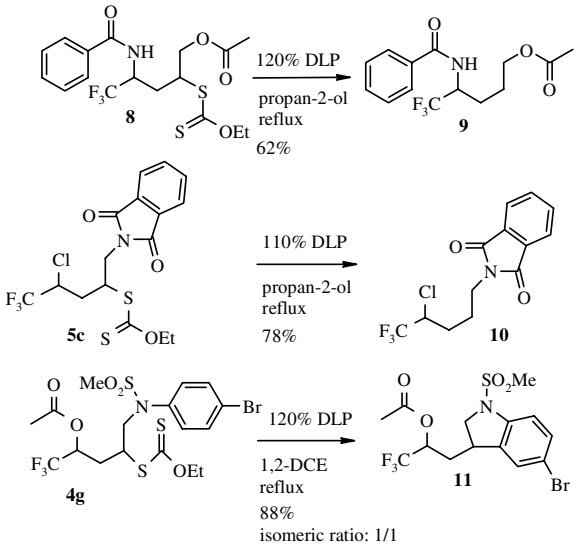
Table 2. Radical additions of xanthate **3** to various olefins

Olefin	Reaction time (h)		Adduct	Yield %	Isomeric ratio
	1.5	**5a**		88	2/3
	1.5	**5b**		74	6/1
	3	**5c**		65	1/1
	3	**5d**[a]		55	1/1
	3	**5e**[a]		27	3/2
	3	**5f**		52[a]	2/1
	5	**5g**		49[a]	1/1
	5	**5h**		28[a]	2/1
	5	**5i**		22[a]	1/1

[a] Yield based on the hemiacetal of trifluoroacetaldehyde (yield over three steps; Xa = S–C(=S)OEt).



Scheme 3. Transformation of adducts.

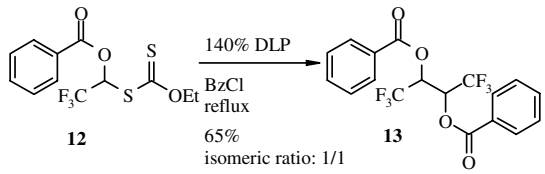


Scheme 4. Radical transformation of adducts.

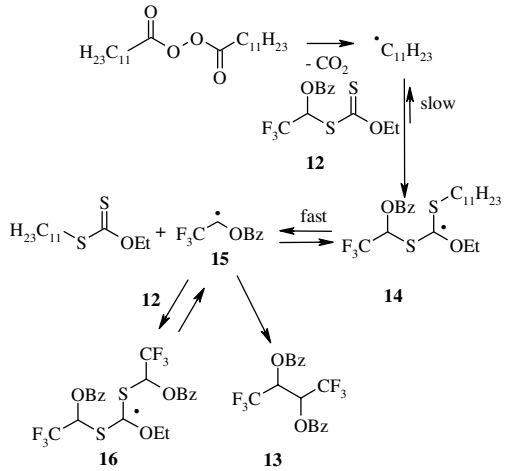
onto the aromatic ring gave the corresponding indoline **11** in 88% yield as a 1/1 mixture of diastereoisomers.[11]

Finally, we found that exposure of the benzoate analogue of reagent **2**, alone, to a stoichiometric amount of dilauroyl peroxide furnished a surprisingly good yield of dimer **13** as a 1/1 mixture of the *meso* and *dl* isomers (Scheme 5).

The benzoate derivative was preferred for isolation purposes. A simple route is thus in hand for accessing a protected form of 1,1,1,4,4,4-hexafluoro-2,3-butanediol, a hitherto not easily available derivative.[12] The formation of dimer **13**, which parallels a similar dimerisation previously observed with acetamido analogue **1**,[1] is not surprising, a priori. What is surprising is the high yield of homo-dimer in a medium that in principle contains other radical species. We have observed such selectivity previously in dimer formation when stabilised radicals such as benzyl radicals were generated using xanthate chemistry.[13] Vidal and co-workers[14] also very recently reported the quantitative formation of a highly substituted dibenzyl dimer when the corresponding xanthate was exposed to stoichiometric amounts of peroxide. These various observations have profound mechanistic



Scheme 5. Dimerisation of xanthate **12**.



Scheme 6. Mechanism for formation of dimer **13**.

implications concerning the xanthate transfer process, which set this method apart from the general Kharasch type atom or group transfer reactions and explain its considerable efficiency and generality. As outlined in Scheme 6, decomposition of dilauroyl peroxide produces undecyl radicals. These rapidly add to the thiocarbonyl group of the xanthate to give **14** and are thus effectively removed from the medium. The reverse reaction is possible but is slow compared to the fragmentation that leads to radicals **15**, since these are more stabilised than simple undecyl radicals.

Three different radicals thus remain in the medium: radicals **15** as well as tertiary radicals **14** and **16**. The last two are stabilised by three heteroatoms, with no possibility for disproportionation, and are quite hindered. They do not therefore participate to any significant extent in radical–radical interactions. This leaves radicals **15** to undergo homo-coupling to give the observed dimer **13**. The presence of the xanthate thus ensures that very few reactive radicals remain in the medium. These radicals are stored as **14** or **16** and are liberated according to their relative stabilities. A sufficiently high concentration of the more stabilised radicals is released to give homo-dimer **13**. Such an automatic regulation of the concentration of the various radicals according to their relative stabilities is not as effective in the case of traditional Kharasch type reactions, where exchange (usually of halides or chalcogenides) occurs in one step.

In the present case, the two-step addition fragmentation, combined with the high radicophilicity of the thiocarbonyl group, results in a very powerful and self-regulating radical transfer process.

In summary, we have described preliminary results that expand vastly our previous study. Access to a large variety of trifluoromethylated structures is now possible using cheap and readily available starting materials. Fluorinated compounds are crucially important to the pharmaceutical and agrochemical industries because of the profound influence that fluorine atoms have on biological activity.[15]

Acknowledgements

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References and notes

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6. *Synthesis of xanthate* **2**: to a solution of 2,2,2-trifluoro-1-methoxy-ethanol (300 mg, 2.31 mmol) in 5 ml of acetone was added portionwise potassium *O*-ethylxanthate (737 mg, 4.62 mmol). The resulting mixture was cooled at 0 °C and sulfuric acid (123.6 μL, 4.62 mmol) was added

dropwise. After 1 h at 0 °C, the mixture was warmed to room temperature, and concentrated under reduced pressure. Ether was then added to the residue to precipitate the excess of xanthate salt, which was removed by filtration. The filtered organic layer was concentrated to give **2a** (351 mg, 69%) as a yellow oil. To a solution of xanthate **2a** in 5 mL of acetone at 0 °C was added dropwise 123.6 μL (2.31 mmol) of sulfuric acid, and then 217 μL (2.31 mmol) of acetic anhydride. After 1 h at 0 °C, the mixture was brought to room temperature, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluant: ethyl acetate–petroleum ether 1/9) to give **2** (372 mg, 89%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (t, J = 5.8 Hz, 3H), 2.21 (s, 3H), 4.71 (q, J = 5.8 Hz, 2H), 7.32 (q, J = 6.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.5, 21.0, 57.6 (q, J = 38 Hz), 70.4, 123.0 (q, J = 280 Hz), 206.9. IR (CCl_4) 2986, 2939, 1778, 1442, 1370, 1344, 1194, 1131, 1032 cm^{-1}. MS (CI + NH_3) m/z 262 (MH+), 279 (MNH_4+).

7. *Typical procedure for radical addition*: n mmol of xanthate and 2n mmol of olefin dissolved in 1,2-dichloroethane (2n mL) were refluxed for 15 min under argon. Dilauroyl peroxide was then added portionwise (5 mol% every 1.5 h) to the refluxing solution. When the xanthate was totally consumed, the crude mixture was cooled to room temperature, the solvent removed under reduced pressure, and the residue purified by flash column chromatography.
8. *Synthesis of xanthate* **3**: xanthate **2a** (1.38 g, 6.3 mmol) and phosphorus pentachloride (1.30 g, 6.3 mmol) were stirred at room temperature for 1 h. The mixture was then concentrated under reduced pressure and purified by flash column chromatography (silica gel, eluent: ethyl acetate–petroleum ether 1/9) to give **3** (270.7 mg, 18%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (t, J = 6.8 Hz, 3H), 4.75 (q, J = 6.8 Hz, 2H), 6.27 (q, J = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 22.6 (q, J = 35 Hz), 71.5, 121.1 (q, J = 280 Hz), 211.1. IR (CCl_4) 2986, 2939, 1442, 1370, 1344, 1194, 1131, 1032 cm^{-1}. MS (CI + NH_3) m/z 239 (MH+).
9. We have found this to be a general method for the introduction of allyl groups starting from xanthates. Briggs, M. E.; Zard, S. Z. *Synlett*, in press.
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